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CASE REPORT

PK/PD model-informed dose selection for oncology phase I expansion: Case study based on PF-06939999, a PRMT5 inhibitor

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Abstract

The optimal dose for targeted oncology therapeutics is often not the maximum tolerated dose. Pharmacokinetic/pharmacodynamic (PK/PD) modeling can be an effective tool to integrate clinical data to help identify the optimal dose. This case study shows the utility of population PK/PD modeling in selecting the recommended dose for expansion (RDE) for the first-in-patient (FIP) study of PF-06939999, a small-molecule inhibitor of protein arginine methyltransferase 5. In the dose escalation part of the FIP trial (NCT03854227), 28 patients with solid tumors were administered PF-06939999 at 0.5 mg, 4 mg, 6 mg, or 8 mg once daily (q.d.) or 0.5 mg, 1 mg, 2 mg, 4 mg, or 6 mg twice daily (b.i.d.). Tolerability, safety, PK, PD biomarkers (plasma symmetrical dimethyl-arginine [SDMA]), and antitumor response were assessed. Semimechanistic population PK/PD modeling analyses were performed to characterize the time-courses of plasma PF-06939999 concentrations, plasma SDMA, and platelet counts collected from 28 patients. Platelet counts were evaluated because thrombocytopenia was the treatment-related adverse event with clinical safety concern. The models adequately described the PK, SDMA, and platelet count profiles both at individual and population levels. Simulations suggested that among a range of dose levels, 6 mg q.d. would yield the optimal balance between achieving the PD target (i.e., 78% reduction in plasma SDMA) and staying below an acceptable probability of developing grade ≥3 thrombocytopenia. As a result, 6 mg q.d. was selected as the RDE. The model-informed drug development approach informed the rational dose selection for the early clinical development of PF-06939999.

JEL CLASSIFICATION

Dose Finding in Oncology (Q4 2023)

Clinical trial registration: clinicaltrials.gov NCT03854227.

INTRODUCTION

Oncology drug development has traditionally relied on the maximum tolerated dose (MTD) approach to select the dose for evaluation of preliminary clinical efficacy or proof-of-concept, as a legacy from the chemotherapy era.[1] With the advent of molecularly targeted agents, there has been a trend to shift away from MTD to dose(s) that offer optimal benefit and risk profile. Selecting the appropriate dose(s) based on data from first-in-patient (FIP) dose escalation is often challenging due to the limited sample size at each dose level, typical heterogeneous study population, and limited efficacy events seen during dose escalation. To address these challenges, model-based data analysis integrating the pharmacokinetics (PKs), pharmacodynamics (PDs), safety, and clinical activity data across a range of dose levels is a powerful tool to maximally extract the information to guide the dose selection.[2] This model-informed drug development (MIDD) paradigm has been increasingly emphasized.[3]

This article describes the application of integrated population PK/PD modeling of the FIP dose escalation data in selecting the recommended dose expansion (RDE) for phase I for PF-06939999, an orally available small molecule inhibitor of protein arginine methyltransferase 5 (PRMT5). The FIP study (NCT03854227) of PF-06939999 includes dose escalation (part 1) and dose expansion (part 2), with the latter part evaluating the safety and tolerability as well as preliminary clinical activity of PF-06939999 at the RDE.

In part 1, 28 patients with various metastatic or advanced solid tumors received PF-06939999 at total daily doses from 0.5 mg to 12 mg once daily (q.d.) or twice daily (b.i.d.); among these patients, 24 were evaluable for dose limiting toxicity (DLT). Two confirmed partial responses were observed, one each at the 2 mg b.i.d. and 4 mg b.i.d. dose levels. Four patients treated with PF-06939999 experienced DLTs: thrombocytopenia ($n = 2$) in the 6 mg b.i.d. cohort, anemia ($n = 1$) in the 8 mg q.d. cohort, and neutropenia ($n = 1$) in the 6 mg q.d. cohort.[4] The most frequent treatment-related adverse events were anemia and thrombocytopenia, which are consistent with the safety profile for drugs in the same class.[5]

Symmetrical dimethyl-arginine (SDMA) is a stable catabolic product of PRMT5 enzymatic activity. In preclinical studies, a correlation between SDMA reduction and tumor response has been established using tumor cell lines[6] and xenograft mouse model (in-house data). In clinical studies, SDMA has been used to monitor levels of PRMT5 inhibition in both peripheral blood and tumor tissues.[5,7] Reduction of plasma SDMA by approximately 78% has been shown to correspond with nearly complete inhibition of tumor SDMA.[7] Therefore, plasma SDMA is used as the PD biomarker for PF-06939999 in this FIP study.

KEY QUESTION

How to choose an appropriate dose for expansion that has a high probability of achieving the target PD effect as surrogate for efficacy while not exceeding an acceptable probability of developing grade ≥3 thrombocytopenia, using an integrated PK/PD modeling approach?

ANALYSIS PLAN AND KEY ASSUMPTIONS

Analysis plan

The population PK/PD analysis included PK, PD, and safety data collected from part 1 of the FIP study, which included 28 patients administered PF-06939999 at the following dose levels: 0.5 mg ($n = 1$), 4 mg ($n = 5$), 6 mg ($n = 6$), or 8 mg ($n = 3$) q.d. and 0.5 mg ($n = 1$), 1 mg ($n = 2$), 2 mg ($n = 3$), 4 mg ($n = 3$), or 6 mg ($n = 4$) b.i.d. The FIP study was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines, defined by the International Council for Harmonization. Patients provided written informed consent. The protocol, amendments, and informed-consent forms were approved by the institutional review board or independent ethics committee. For more detailed description of study design and sampling schedule for PK, SDMA, and platelet counts, please see Appendix S2.

All PK and PD data were used for the population PK/PD analysis except observations from unplanned visits, end of treatment, or missing actual collection time. Below the limit of quantification (BLOQ) PK data accounted for <10% of PK observations (3% were postdose PK samples) and none of the PD data were BLOQ. Therefore, all BLOQ PK data were excluded from the analysis. The PK of PF-06939999 was adequately described using a two-compartmental model with first-order absorption. Individual PK parameter estimates from the final population PK model were used in subsequent PK/PD modeling for SDMA and platelet counts. The log-transformed SDMA time course data were described using an indirect response PD model with saturable inhibition on SDMA production. The time course of platelet counts was modeled using a semimechanistic PK/PD model developed by Friberg et al[8] with a linear drug effect on the proliferation rate and three transit compartments. An exponential model was used to model the interindividual variability for all PK and PD models, and to model the residual error for both PK and thrombocytopenia PD models. An additive residual error model was used for the SDMA PD model. Model structure is presented in Figure 1. Model development and evaluation details are described in the Appendix S1.

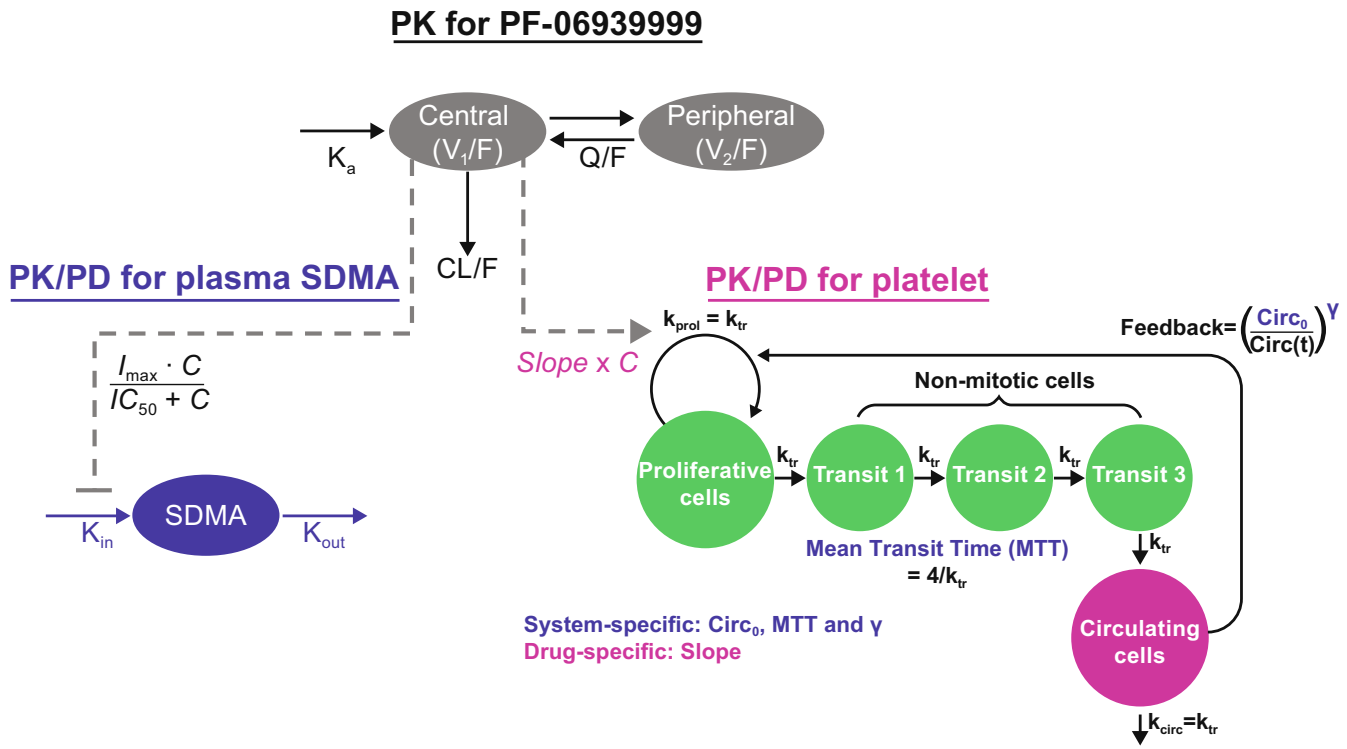


FIGURE 1 PK/PD (SDMA and platelet) model structure for PF-06939999. *PK model*: CL/F, apparent clearance; F, bioavailability; K_a, rate of absorption; Q/F, apparent inter-compartment clearance; V/F, apparent volume of distribution. *PK/PD model for plasma SDMA*: C, plasma concentration of PF-06939999, I_{max}, maximum inhibition; IC_{50}, PF-06939999 concentration that produces 50% of maximum inhibition; k_{in}, zero order production rate of the response; k_{out}, first order elimination rate of response. *PK/PD model for platelet*: $CIRC_0$, circulating platelet count at baseline; $CIRC_t$, circulating cell counts at time *t*; γ, feedback parameter; K_{circ}, rate of physiological elimination of circulating cells; K_{prol}, rate of cell proliferation; K_{tr}, rate of transit between compartments; MTT, mean transit time, which represents the time for a committed stem cell to pass through the maturation compartments in the bone marrow before entering the circulation; slope, linear drug effect on platelet proliferation. PK/PD, pharmacokinetic/pharmacodynamic; SDMA, symmetrical dimethyl-arginine

Simulations were performed using the final PK/PD parameters to predict the steady-state plasma SDMA reduction from baseline (expressed as percentage) and the nadir platelet count following 0.1–12 mg total daily dosing. This range covers the dose levels (expressed as total daily dose) tested during dose escalation. The probability of achieving the target PD response (i.e., 78% SDMA reduction from baseline) and grade ≥3 thrombocytopenia (defined as platelet count $\leq 50 \times 10^9$/L per National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0) was summarized at the following dose levels: 4 mg q.d., 6 mg q.d., and 8 mg q.d.

Key assumptions

Thrombocytopenia was chosen as the safety end point in this modeling work as it represented the main adverse event of concern in the dose escalation part. Plasma SDMA, the peripheral PD marker for PRMT5 inhibition, was used as a surrogate for efficacy in this modeling work due to limited clinical efficacy events observed. A 78% reduction from baseline in plasma SDMA levels was expected to result in sufficient target engagement, as it was associated with near complete loss of tumor SDMA previously reported.[7] For the investigation agent without wide therapeutic index, ≥G3 thrombocytopenia in 30%–35% patients was considered as acceptable clinical safety for patients with metastatic disease.

Details of the modeling and simulation software and NONMEM control file for the final PK/PD model are included in Appendix S1.

RESULTS AND DISCUSSION

This PK/PD analysis included 400 PK observations, 247 SDMA observations, and 221 platelet count observations from 28 patients across nine dose levels. Summary of patient characteristics are shown in Table S1. The small sample size would limit the interpretation of covariate analysis, which did not find baseline body weight, age, or hepatic function as potential significant covariates (i.e., change in objective function value <3.84).

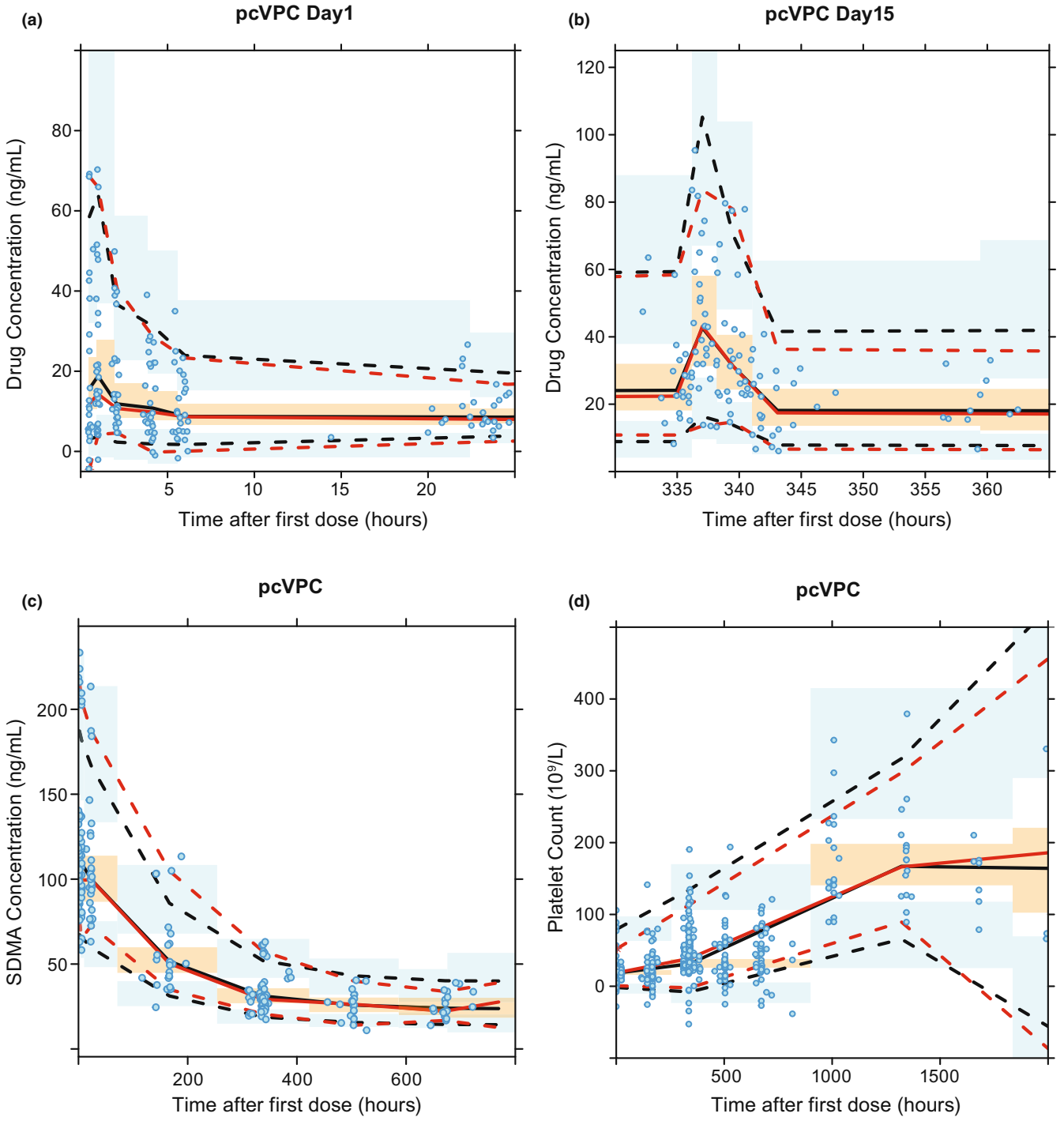


FIGURE 2 Prediction- and variance-corrected visual predictive check for the final PK/PD model. (a) PK profile on cycle 1 day 1; (b) PK profile on cycle 1 day 15; (c) plasma SDMA profile; (d) platelet count profile. The blue scatter points represent the observed data. The red and black lines represent the median (solid line), 5th percentile (lower dash line), and 95th percentile (upper dash line) of the observed and simulated data, respectively. The orange and the light-blue shaded area represent the 95% confidence interval of simulated median and 5th and 95th percentiles, respectively. Simulation was performed for 5000 participants. pcVPC, prediction-and variance-corrected visual predictive check; PD, pharmacodynamic; PK, pharmacokinetic; SDMA, symmetrical dimethyl-arginine

The final PK and PD models described the data well, as demonstrated by the goodness of fit plots in Figures S1–S3. No indication of model misspecification was evident, especially considering the small number of patients in the dataset. The prediction- and variance-corrected visual predictive check plots (Figure 2) suggest that the final PK and PD models adequately described the data, including the central tendency and the variability of the observations. Comparisons of prediction versus observation stratified by dose levels are presented in Figures S4 and

TABLE 1 PF-06939999 PK and PD (SDMA and platelet count) model parameters

Parameter (unit)	Estimate	RSE (%)	IIV (%)	RSE (%) of ω^2	IIV Shrinkage (%)
PK model					
CL/F (L/h)	9.53	8.94	38.9	41	2.52
V_1/F (L)	160	16.5	61.1	25	5.74
Q/F (L/h)	26.2	15.3			
V_2/F (L)	285	8.25			
K_a (h^{-1})	2.31	27			
Scaling factor for F	0.647	14.7	53.6	33	23.2
PK residual error	0.112	12.2			
SDMA PD model					
I_{max}	0.823	1.27			
IC_{50} (ng/ml)	0.425	18.1			
K_{out} (h^{-1})	0.00708	5.15			
Baseline SDMA (ng/ml)	113	5.59	29.1	28.3	−0.862
SDMA residual error	0.0146	19.2			
Platelet count PD model					
MTT (h)	134	7.66			
Slope	0.00496	14.2	52.2	61.1	18.3
Feedback, γ	0.217	19.5	46.9	47.7	20.4
Baseline PLT (10^9/L)	232	5.76	28.3	34	2.85
PLT residual error	0.0235	19.3			

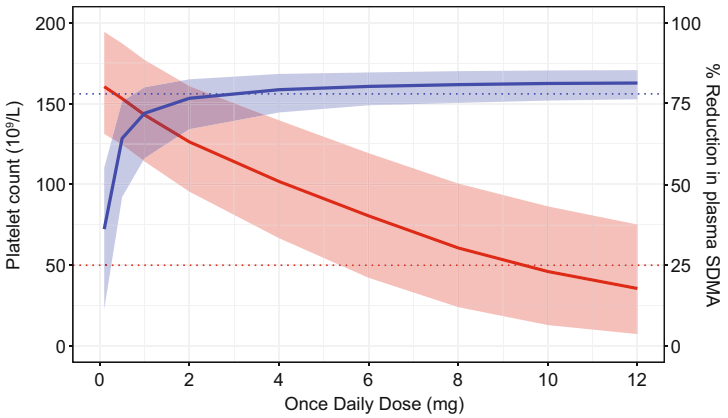
Note: A scaling factor for F was introduced to account for the apparently lower bioavailability for doses ≤6 mg/day (dose-dependent F) in day 1 (time-varying F).

Abbreviations: CL/F, apparent clearance; F, bioavailability; IC_{50}, drug concentration that produces 50% of maximum inhibition; IIV, interindividual variability; I_{max}, maximum inhibition; K_a, rate of absorption; K_{out}, first order elimination rate of response; MTT, mean transit time; PD, pharmacodynamic; PK, pharmacokinetic; PLT, platelet count; Q/F, apparent intercompartment clearance; RSE, relative standard error; SDMA, symmetrical dimethyl-arginine; SE, standard error; V_1/F, apparent volume of distribution for central compartment; V_2/F, apparent volume of distribution for peripheral compartment; ω^2, variance of interpatient variability.

S5. Overall, model simulations reproduced the observed PK and PD profiles well. The final parameter estimates are presented in Table 1. The estimates for system-specific parameters were physiologically plausible. The model-estimated typical value of baseline SDMA was close to the arithmetic mean of observations (117 ng/ml). For the thrombocytopenia model, all the system-specific parameters are within the range of reported values: 37–134 h for MTT,[9] 114–255 10^9/L for baseline platelet count,[9,10] and 0.14–0.29 for feedback, γ.[9] The condition number and shrinkage for ETA and EPSILON were acceptable according to the criteria set in Appendix S2.

Simulations were performed for a range of q.d. doses using the final PK/PD parameters (Figure 3). The q.d. regimen was of interest for simulation because of the similarity in the observed peak-to-trough ratio between b.i.d. (~2.1-fold) and q.d. (~2.8-fold) and the preference of a q.d. regimen for patient convenience and better compliance. Simulations suggested that plasma SDMA inhibition plateaued above 4 mg q.d., whereas the platelet count nadir continued to drop with further increase in dose. The probabilities of reaching the target PD effect and of developing grade ≥3 thrombocytopenia are summarized for three dose levels of interest in Figure 3. Compared with 6 mg q.d., the 8 mg q.d. dosage would provide minimal incremental benefit of SDMA inhibition while resulting in an undesirable probability of developing grade ≥3 thrombocytopenia. On the other hand, 4 mg q.d. would carry the risk that around one third of patients may not reach the PD target. Therefore, 6 mg q.d. was considered to be an optimal RDE to offer the maximum benefit-to-risk ratio for patients, based on the integrated PK/PD and clinical safety analysis. In addition, the median predicted exposure at 6 mg q.d. (including average and trough concentrations on day 15) was within the range of exposure at which the two partial responses were observed, serving as supportive evidence given the limited sample size.

Based on the totality of data, including PK, PD, efficacy, and safety, 6 mg q.d. was chosen as the dose for the FIP monotherapy expansion.



	4 mg	6 mg	8 mg
Probability of target PD	64%	76%	81%
Probability of grade ≥3 thrombocytopenia	17%	30%	43%

FIGURE 3 Simulated dose–response (SDMA and platelet count) relationship. Blue line and shaded area represent median and 90% prediction interval of percentage reduction of plasma SDMA at steady-state from baseline; red line and shaded area represent median and 50% prediction interval of platelet nadir at steady-state. Simulated data were based on 5000 simulations. Red horizontal dashed line represents threshold for grade 3 thrombocytopenia; blue horizontal dashed line represents the target SDMA reduction from baseline (i.e., 78%). PD, pharmacodynamic; SDMA, symmetrical dimethyl-arginine

Impact assessment

The PK/PD model informed the selection of the FIP expansion dose, which aims to maximize the potential of clinically relevant target engagement while being safe and tolerable. This quantitative analysis has added confidence in dose selection based on the limited and heterogeneous data from FIP dose escalation and avoided the need for exploring multiple dose levels in expansion.

During early clinical development of oncology therapeutics, given the uncertainty in the outlook for the investigational agent/drug target and the need for rapid decision making, the phase I dose expansion often tests only one dose level for assessment of preliminary signs of efficacy and go/no-go decisions. In fact, only ~20% of the new-molecular entities approved between 2010 and 2021 had tested more than one dose or dose regimen beyond the phase I dose escalation.[11] Data from different dose cohorts could consist of different dosing frequencies, treatment duration, relative dose intensity, and potentially a wide range of doses. The fit-for-purpose semimechanistic PK/PD model considers the actual dosing record for individual patients and is useful in integrating heterogeneous data under variable actual dosing conditions. It has the advantage over the MTD approach in dose selection by considering safety events that occurred outside of the DLT observation window and toxicity of lower grade. In addition, the model can be used to simulate different dosing scenarios (e.g., continuous vs. intermittent dosing) to guide future dose exploration if needed.

The goal for MIDD in this scenario is to integrate all relevant information to facilitate quantitative dose decision making. We present here one such example that used fit-for-purpose models to enable the rapid RDE decision. Additional model features were explored, including different numbers of transit compartments for the thrombocytopenia model, error model, and data transformation, but did not improve model fitting based on the current analysis. The models may be further refined as clinical data accumulate. The major limitation of this PK/PD modeling and simulation work was the uncertainty in the estimated variability based on a small dataset. Despite this limitation, modeling-based data analysis is a powerful approach that can maximize the value of the often sparse and heterogeneous data from a limited number of patients to inform the dosing regimen.

CONCLUSION

The fit-for-purpose population PK/PD modeling analyses of the FIP dose escalation data have informed the rational selection of the dose for FI expansion for PF-06939999, and demonstrates the value of MIDD in early clinical development of oncology drugs.

AUTHOR CONTRIBUTIONS

All authors wrote the manuscript. Designed and performed the research: Kai H. Liao, Meng Li, I-Ming Wang, Donghua Yin, and Cen Guo. All authors analyzed the data.

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CONFLICT OF INTEREST

C.G., N.S., M.L., I.W., and D.Y. are employees of Pfizer and hold Pfizer stock or stock options. K.L. was an employee of Pfizer.

DATA AVAILABILITY STATEMENT

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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